Nicotine has suppressive effects on dendritic cell function

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Cigarette smoking is a major health hazard which increases the risk of cancer, particularly lung cancer, as well as cardiovascular and respiratory disease. Damage to the immune response is considered to underlie many problems provoked by smoking, and alteration in responsiveness of smokers' leukocytes has been recorded.[1] For example, T cells proliferate less readily to mitogens, natural killer (NK) cells have reduced activity against tumour cell lines and alveolar macrophages from smokers release lower levels of cytokines and have a reduced ability to phagocytose. The effects of cigarette smoke on the immune response are mimicked by nicotine. The average cigarette contains 10 mg of nicotine and between 1 and 2 mg are delivered to the lungs when a cigarette is smoked with highly variable amounts achieved in the smoker's blood.[2]

Dendritic cells (DCs) are the body's key antigen presenting cells that are pivotal in the initiation of a primary immune response. DCs deliver not only antigen/major histocompatibility complex (MHC) and costimulatory signals to T cells but also a third class of signal comprising soluble cytokines which are influential in determining the class of mature T cell. Through release of the cytokine interleukin (IL)-12, DCs polarise naive T-cell maturation towards a IFNγ-producing T helper (Th)1 type of T cell required for cell-mediated responses against invading pathogens or potentially tumours.[3,4] Other DC-associated factors such as IL-10 and prostaglandin E2 (PGE2) can suppress IL-12 release and skew maturation toward T cells of the Th2 type which determine B cell responses.

In this issue of Immunology, Nouri-Shirazi and Guinet provide the first evidence that nicotine has a selective effect on monocyte-derived human DC function which leads to suppression of Th1 polarisation.[5] The first pertinent observation is that the antigen capture mechanisms of DCs are compromised as nicotine causes a decrease in mannose receptor expression linked to a five-fold drop in receptor-mediated endocytosis. In addition, phagocytosis of apoptotic cells is reduced by two-fold, but there are no problems with macropinocytosis. Thus there is a deficiency in the first step in the defence against microorganisms, which involves pathogen uptake by the sentinel DCs scattered throughout the tissues.

Lipopolysaccharide (LPS), which mimics exposure to Gram negative bacteria, causes DC maturation. In the presence of both nicotine and LPS, DCs displayed a 60% decrease in IL-12 release although many other features of maturation were expressed normally, including CD80 and CD86 (signal 2) and CD40 which facilitates cytokine production. Given the pivotal role of IL-12 in directing T-cell maturation, it was expected that T-cell responses would be adversely affected and, indeed, three major defects were recorded. Firstly, DC-dependent T-cell proliferation was substantially reduced. As DC-independent control of proliferation induced by CD3/CD28 mAbs was similar between nicotine treated and untreated cultures, the result suggested a DC and not T cell problem. Secondly, nicotine exposed T-cell cultures had a 63% reduction in release of IFNγ. Importantly the T cells had not simply been rendered anergic as IL-2, IL-4 and IL-10 release was normal. The final point made by the study was that restimulation of nicotine-exposed T cells by fresh DCs failed to restore their ability to respond normally indicating long lasting effects on Th1 responses.

Overall the finger points to a nicotine-induced impairment in ability of DCs to direct complete Th1 polarisation of naive T cells during the priming phase. The negative effect of nicotine on receptor-mediated uptake of antigen, with the subsequent diminishment in IL-12 may be responsible for the observed problems. It was therefore a reasonable speculation that the above immune aberrations in T-cell activity would be overcome by addition of IL-12 into the primary cultures. However, the authors state that such treatment failed to have a corrective effect suggesting that there are other nicotine-mediated effects on DCs still to be identified. This may also explain the impaired ability of nicotine-exposed DC to drive T-cell proliferation that is likely to be unrelated to the failure to produce IL-12. It would also have been interesting to have profiled Th2 responses under a similar nicotine exposure regime. Elevations in Th2-inducing factors such as PGE2 and IL-10 and immunosuppressive factors such as transforming growth factor (TGF)β have been recorded in human tumours.[6] In summary, the distinctive package of effects which nicotine has on the central players in the adaptive immune response makes it an intriguing effector molecule to study, quite apart from the profoundly negative effects that it has on human health.

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